Remarks

Claims 1-21, 31, 35-38, 40-45, 47, 49 and 75 were pending in the application. Claims 1, 4, 5, 6, 47 and 75 have been amended, and new claims 76-83 added for consideration. Hence claims 1-21, 31, 35-38, 40-45, 47, 49 and 75-83 are pending.

Support for Claim Amendments

No new matter has been added by this amendment. Support for the claims amendments is shown below:

Amended claim 1 is supported, for example, at page 13, lines 21-24 (sample fluid flows through the test strip); page 16, lines 16-17 (sample migrates through porous material of the collection member); and page 24, lines 26-30 (tracer applied to test strip in presence of delayed release agent); page 35, lines 3-8 (tracer mixed with sucrose delayed release agent and applied to substrate); page 36, lines 12-14 (tracer mixed with buffer containing sucrose delayed release agent and applied to substrate); and page 37, lines 28-30.

Amended claim 4 is supported, for example, at pages 17-18, particularly page 17, lines 23-24 ("bibulous collection member 122 with a flat proximal edge 124 and a flat distal edge 126") and page 18, lines 9-10 ("the analyte-tracer conjugate is dried in mobilization zone 154 on strip 120 prior to pad 132 being applied to support 128"). See also page 35, lines 5-9; page 36, lines 13-16; and page 37, lines 28-32 (tracer applied to substrate and allowed to dry)

Claim 5 has been amended to provide better antecedent support for "the pores", and the amendment is supported, for example, by the inherent meaning of a porous material, as well as at page 21, line 15 (discussing pores in the test strip).

Amended claim 6 is supported, for example, at page 17, lines 22-23 (test strip is bibulous collection member 122) and page 18, lines 3-10 (collection member contains the mobilization zone, primary capture area and secondary capture area, and the tracer is dried in mobilization zone 154 of the test strip).

Amended claim 11 is supported at page 18, lines 9-10.

Amended claim 47 is supported is supported at page 18, lines 9-10 and 14-15 and FIG. 1B (conjugate dried in mobilization zone beneath surface of test strip) as well as in the examples

in which the conjugate is applied in a liquid to the test strip and allowed to dry. Support is also found at page 18, lines 16-26 (sample is applied to pad and migrates through the mobilization zone to the primary capture area).

Amended claim 75 is supported as in claim 1 and is supported at page 36, lines 19-21 and at page 24, lines 12-13 where the tracer is described as below the pad *or* distal to it; claim 78 is supported at page 36, lines 19-21 (where only one of the four conjugate/tracer lines was overlapped); claim 79 is supported at page 36, lines 19-21; claim 80 is supported at page 24, lines 11-13 (tracer can be distal to the application zone). Claims 81-83 are similar to pending claims 9-10.

Response to Rejections under Section 112

Claims 1-21, 31, 35-38, 40-45, 47 and 49 were rejected under 35 U.S.C. Section 112, first and second paragraphs, because it was said that there was no support for the bibulous substrate selectively delaying migration of the detectable tracer. Although applicant disagrees with that conclusion, the language has been amended from the claims to simplify issues and advance prosecution.

Claim 5, line 2, was said to be vague because the term 'sufficiently smaller" was unclear. Applicant points out that the claim itself provides the definition of "sufficiently smaller" as allowing the detectable tracer to migrate along the path of liquid flow more slowly than the analyte. However, to advance prosecution, the word "sufficiently" has been removed from the claim.

Prior Art Rejections

35 U.S.C. Section 102 Rejection over Boehringer et al.

Claims 1, 2, 12, 13, 20, 21, 31, 35, 36, 40, 41, 45 and 49 were rejected under 35 U.S.C. Section 102 as anticipated by Boehringer et al. (WO98/39657). The basis of the rejection is that Boehringer inherently anticipates the referenced claims because Boehringer inherently includes features that could under some circumstances produce the presently claimed invention. Applicants have previously submitted declaration evidence and argument showing that Boehringer does not necessarily provide an assay in which the analyte migrates through the

porous material of the bibulous substrate ahead of the detectable tracer, and the PTO has acknowledged that it "is quite possible for the detectable tracer and analyte to reach the primary capture area together." As noted in the December 4, 2006 response, it is therefore not possible for Boehringer to inherently anticipate or render obvious the claimed invention.

However, to advance prosecution, applicant has amended the pending claims to specify particular structural features that further distinguish the cited references. Claim 1, for example, states that the "bibulous substrate is a porous material to which the detectable tracer has been applied in the presence of a delayed release agent." The remaining claims 2, 12, 13, 20, 21, 31, 35, 36, 40, 41, 45 and 49 depend either directly or indirectly from claim 1. Since Boehringer does not disclose a test strip in which the detectable tracer is applied to the bibulous, porous substrate in the presence of a delayed release agent, these claims are not anticipated.

The amended claims are not obvious for the reasons set out in the next section of this reply.

35 U.S.C. Section 103(a) Rejection

Claims 3-5, 8-10 and 75 were rejected as being obvious over Boehringer et al. in view of Attridge (U.S. Patent No. 5,631,170). The Attridge reference discloses an optical biosensor that uses the principles of internal reflection spectroscopy (col. 1, lines 15-17). Light is shined through the transparent waveguide material and is totally internally reflected in the medium of the waveguide to generate an electromagnetic waveform that helps identify interaction between an analyte and the immobilized agent on the surface of the waveguide. The immobilized reagent on the surface interacts with an analyte in a sample solution that is flowed external to the waveguide. The waveguide substrate material is a transparent material (col. 12, line 47) that must not have surface roughness or bulk inhomogeneities that scatter the excitation light that shines through the transparent waveguide (col. 1, line 57 to col. 2, line 7). Attridge is quite explicit that it would be "desirable to reduce or eliminate" such sources of imprecision (col. 1, lines 57-59).

The Office action notes that Attridge discloses that a labeled analog may be provided as an ancillary agent that can be contained within a dissoluble layer that includes a capping reagent that delays dissolution of the reagent. However, in all instances, the reagents are carried on the

surfaces of the waveguide plates (see col. 12, line 60 to col. 13, line 5). In all instances, the waveguides are rigid transparent materials, such as plastic, quartz, silica or glass (col. 12, lines 46-54). The ancillary reagent is released from the surface of the waveguide into the liquid that flows over it so that the ancillary reagent can provide a reference signal that is detected by the light that shines through the waveguide.

The Office action states that Attridge teaches that delayed release provides an opportunity to measure a reference signal that is reflected through the transparent waveguide, and further that Attridge discloses that the ancillary reagent can be used in devices such as a 'test strip." However, the patent actually teaches that the disclosed method can be performed with a "test strip biosensor" (col. 5, lines 28-32) by which is clearly meant a waveguide biosensor that is dipped into an analyte like a test strip. This patent does not disclose, suggest or in any way contemplate the use of a delayed release capping agent with anything other than the transparent waveguide biosensor disclosed in the Attridge patent. Specifically, there is no teaching about using the capping agent in a bibulous lateral flow device in which a sample liquid flows through the test strip instead of over it. Also, the claimed test strips do not measure a spectroscopic reference signal from a waveguide; one skilled in the art would not consider incorporating the capping reagent of Attridge into a device that does not measure a spectroscopic reference signal. Therefore the rationale provided by the Office action for making the combination does not provide a motivation to a person of actual skill in the art. It would make no sense to use the spectroscopic reference reagent in a device for which it is neither intended nor suitable.

Claim 1

Claim 1 of the present application is directed to a test strip in which the sample application area, mobilization zone and primary and secondary capture area are in a path of liquid flow through a bibulous (absorbent) substrate. The mobilization zone comprises a porous material to which the detectable tracer has been applied in the presence of a delayed release agent so that the analyte migrates through the porous material of the bibulous substrate ahead of the detectable tracer. The Office action has suggested that it would be obvious to incorporate the capping layer of Attridge on the test strip of Boehringer because Attridge discloses that the capping layer delays release of an ancillary reagent into the liquid passing over the transparent

wave guide. The Office action further asserts it would be obvious to use the capping layers of Attridge in the lateral flow device of Boehringer, and predictable that it would work for that purpose, because Attridge suggests that the capping layer could be used in a test strip biosensor. Applicants disagree and request reconsideration because the references do not establish a prima facie case of obviousness.

To establish a prima facie case of obviousness, the combined references must teach or suggest all the claim limitations, and there must be some suggestion or motivation to modify the references. See MPEP 2142. The cited references do not satisfy either requirement of the prima facie case.

One skilled in the art would not consider making the proposed combination. First, Attridge clearly and repeatedly teaches that his test relies on a homogenous waveguide through which internal reflection must occur for the spectroscopy signal to be read. One skilled in the art would consider it counter-intuitive to even consider using a non-transparent, non-homogenous substrate of the type disclosed in Boehringer. The reference to a "test strip" in the Office action (citing Attridge at col. 5, lines 28-30) is incomplete, because the actual phrase used by Attridge is a "test strip biosensor" which clearly refers to a waveguide biosensor that is dipped in a sample. One skilled in the art would have no expectation of success that the capping layer of Attridge that provides a spectroscopic reference signal would have any function on the lateral flow test strip of Boehringer because a) a bibulous porous lateral flow test strip in Boehringer is not transparent or homogenous and would not provide the required total internal reflection; b) the Boehringer substrate violates Attridge's explicit teachings about the required features of a good waveguide set forth at col. 1, line 57-col. 2, line 7; c) a "reference signal" (wavelength change in an internally reflected light source) is not measured in Boehringer, so one of skill in the art would have no motivation to use the Attridge capping layer to provide "more accurate referencing" as suggested in the Office action; d) the use of a bibulous, porous substrate would defeat and frustrate the function of the Attridge waveguide invention, because a bibulous test strip would absorb the liquid flowing over it, and the porosity of the strip would produce gross disruptions of homogeneity that Attridge teaches are essential for the proper functioning of its waveguide. A person of skill in the art would not be motivated to use the capping reagent of

Attridge to provide a spectroscopic reference signal in a lateral flow assay that is unrelated to and unsuitable for the use of the reference reagent or the signal it provides.

Even if one did make the asserted combination, the claimed invention would not be produced. Claim 1 calls for a path of liquid flow *through* a bibulous substrate wherein the mobilization zone comprises a *porous* material to which the detectable tracer has been applied in the presence of a delayed release agent. The capping agent in Attridge sits on top of a waveguide that by definition must exclude liquid (to avoid introducing heterogeneities that interfere with spectroscopic analysis). The path of liquid flow in Attridge is over the substrate, and not through it as claimed. The capping agent is external to the waveguide, and if combined with Boehringer would produce a substrate in which the capping agent was on top of and external to the substrate, where it would not affect the tracer and analyte as they migrated *through* the bibulous substrate. In contrast, claim 1 calls for a bibulous substrate in which the mobilization zone is a porous material on which the tracer has been applied in the presence of the delayed release agent, and the porous material would by definition absorb the liquid into it so that the tracer does not sit on the surface like the "cap" of Attridge.

The absorption of the tracer into the bibulous, porous substrate is a significant distinction between the cited references and the prior art. The presence of the tracer within the bibulous porous substrate is a feature that, in combination with the delayed release agent, helps delay migration of the tracer through the test strip so that the analyte reaches the primary capture zone before the tracer. As already demonstrated by applicants, this delay improves the sensitivity of the lateral flow assay performed on the bibulous substrate.

The Office action also cited Fredrickson et al. as allegedly showing a lateral flow matrix in which a tracer is positioned beneath a sample application zone. However, Fredrickson is devoid of any disclosure or suggestion that the tracer be applied in a porous mobilization zone in the presence of a delayed release agent. One skilled in the art would not be led to use the capping agent of Attridge with the bibulous porous test strip of Fredrickson for the same reasons as discussed above in connection with the combination of Attridge with Boehringer et al. However, the combination would be even more far-fetched with Fredrickson in which the conjugate pad 3 is already underneath a sample application pad that would interfere with application of the capping agent to it, release of the capping agent from it, and would interfere

with the spectroscopic measurements of Attridge that are facilitated by the capping agent of that reference.

There mere existence of the delayed capping reagent in Attridge does not establish a prima facie case of obviousness in the absence of a motivation in the art to use the Attridge wave guide cap with the lateral flow test strip of either Boehringer et al. or Fredrickson, and an expectation of success that it could be used to improve the sensitivity of those tests. Attridge's quoted reference to using the cap in a "test strip biosensor" is clearly not a suggestion to use it in a lateral flow assay of the type that is claimed here. Moreover, the Office action has not explained how one skilled in the art would be motivated by Attridge to improve the lateral flow assay test, or how it would even function if the references were combined. A prima face case of obviousness has not been established with respect to the amended claim.

Claim 11

Claim 11 was rejected over Boehringer et al. and Attridge in view of Fredrickson or Schramm. The Office action contends that it would be obvious to use the cap of Attridge's wave guide with the lateral flow test strip of Boehringer et al., and put the cap under the sample application zone as in Fredrickson or Schramm. The rationale for such a complex combination was that Fredrickson and Schramm taught advantages for impregnation of the conjugate into the bibulous test strip.

Schramm does not show a mobilization zone below the sample application zone. It therefore fails to establish a prima facie case with respect to claim 11.

The proposed combination of Boehringer et al. with Attridge and Fredrickson would not be obvious because one of skill in the art would not place the Attridge cap under a sample application zone. Although the Office action suggests that such a motivation would be found in Attridge's teaching that the cap increases sensitivity of the wave guide device, one of skill in the art would be perplexed by the suggestion that the cap would improve the sensitivity of a lateral flow device, particularly if the cap were below the sample application zone. Such a placement of the cap would interfere with the release of the cap into the liquid that flows over a waveguide and into which the ancillary agent under the cap is released to provide a reference signal. One of

skill in the art would have no expectation that a workable device could be made by randomly combining such disparate technologies, as suggested in the Office action.

Claim 31

Claim 31 is a method claim that depends from claim 1, and is allowable for the same reasons set forth in connection with claim 1.

Claim 47

Claim 47 was rejected as obvious over Boehringer et al. in view of Fredrickson or Schramm. Amended claim 47 states that the detectable tracer is dried beneath an external surface of the test strip and the sample application area is a pad that is applied over the detectable tracer on the strip. None of the cited references disclose such a structure.

The conjugate pad 3 in Fredrickson is a pad impregnated with conjugate that is layered on top of an underlying test strip. This overlapping conjugate pad differs from the claimed invention because the layering of the conjugate pad of Fredrickson on top of the test strip dispenses the conjugate from the mobilization zone on to the top of the test strip instead of below its external surface. The placement of the overlapping conjugate pad dispenses the conjugate externally on the surface of the test strip instead of within the interior of the test strip where its migration will be slowed relative to the analyte.

Similarly, Schramm does not disclose a sample application area pad that is applied over the detectable tracer dried on the strip.

The cited references do not disclose the claimed test strip, and the claim is allowable.

Claims 75-83

Claim 75 includes the limitation that the test strip comprises a bibulous substrate in which release of the detectable tracer is delayed relative to movement of analyte through the bibulous substrate by a delayed release agent in the mobilization zone. The path of liquid flow moves *through* the bibulous substrate from the sample application area and the mobilization zone to the primary and secondary capture areas, wherein the release of the detectable tracer from the bibulous substrate is delayed by the delayed release agent relative to movement of the analyte.

This claim was rejected over the combination of the lateral flow assay of Boehringer et al. in view of the wave guide strip biosensor of Attridge. It would not be obvious to use the wave guide cap of Attridge on the lateral flow test strip of Boehringer et al. for the reasons discussed in connection with claim 1 above. Also, if the combination were made it would not produce the claimed invention in which liquid flows along a path of liquid flow through the mobilization zone to the primary capture area. Attridge only discloses placing a cap on top of a substrate over which liquid flows without entering the substrate. The combination neither discloses nor suggests a delayed release agent through which a path of liquid flow moves.

Claims 76-80 add additional limitations that are not shown in the references. A prima facie case of obviousness has not been established with respect to these claims. Claims 81-83 depend from claims that are allowable, and further define allowable subject matter.

Conclusion

It is believed that the claims are in condition for allowance. If any matters remain before the claims are allowed, applicant requests that the examiner call the undersigned to address those matters in a telephone interview.

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